

BRIEF COMMUNICATIONS

Risk of Subsequent Cancer Following Breast Cancer in Men

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The etiology of breast cancer in men is not well understood. We assessed the risk of subsequent cancers among all 1788 men diagnosed with a first primary breast cancer from 1973 through 1996 who were registered with the Surveillance, Epidemiology, and End Results (SEER) Program. Although the overall subsequent cancer risk in men was not increased (standardized incidence ratio [SIR] = 0.99, 95% confidence interval [CI] = 0.86 to 1.1), the risk of contralateral second breast cancer was strongly elevated (12 cases; SIR = 30, 95% CI = 15 to 52). The risk was higher for men diagnosed with their first breast cancer before age 50 years than for older men. There were no major differences in the risk of contralateral breast cancer associated with different treatments received for the first breast cancer. The relative risk of second breast cancer was substantially higher among men than among women with breast cancer, but the absolute excess risk was lower. We conclude that men diagnosed with breast cancer are at high risk of contralateral breast cancer. [J Natl Cancer Inst 2002;94:1330-2]

Breast cancer among men is relatively rare, with an age-standardized incidence rate of about 1 per 100 000 person-years in most countries and approximately 1% of the incidence rate among women (1). Geographic and temporal variation in the rates is modest, suggesting limited environmental and life-style influence (2). However, international comparisons have shown some association in breast cancer rates between men and women (3,4). Although

the etiology of breast cancer in men is not well understood, hormonal and genetic factors both appear to play a role. Similar to that of breast cancer in women, an increased risk of breast cancer in men has been associated with a family history of breast cancer (5,6). Additional known or suspected risk factors include hormonal abnormalities, such as Klinefelter's syndrome, gynecomastia, testicular disease, liver cirrhosis, and treatment with exogenous estrogens (7,8). To gain insight regarding the etiology of breast cancer in men, we conducted a follow-up study of the risk of subsequent cancers among men with breast cancer.

We evaluated the risk of a subsequent cancer among 2-month survivors who were diagnosed with a first primary cancer from 1973 through 1996 and reported to the nine Surveillance, Epidemiology, and End Results (SEER)¹ Program cancer registries. SEER registry incidence files were searched for a second primary cancer that developed at least 2 months after the diagnosis of a first primary cancer. For each patient, person-years at risk (PYR) were accrued 2 months after the first primary breast cancer diagnosis (to avoid detection bias due to staging procedures) until the date of death, date of last follow-up, date of diagnosis of subsequent primary cancer, or study end, whichever came first. Age-specific, sex-specific, and calendar-specific incidence rates for all cancers combined and for specific cancer sites were multiplied by the appropriate person-years to compute the expected number of cancers. Two-sided tests for statistical significance of the standardized incidence ratios (SIRs, ratio of the observed-to-expected number of subsequent cancers) and exact 95% confidence intervals (CIs) were calculated assuming that the observed number of second cancers followed a Poisson distribution, as described (9). Absolute excess risks (AERs) were calculated as observed minus expected numbers of cancers divided by the PYR and were expressed as the number of excess cases per 10 000 PYR.

Of the cancers identified from 848 863 male patients, 96% of the first and 95% of the second primary cancers (99% and 97% of breast cancers from men, respectively) were histologically confirmed. The cohort included 1788 men with a first primary breast cancer,

none of whom had bilateral disease. The mean age at diagnosis was 65 years for all men with a first primary cancer and 66 years for men with breast cancer (the medians were 67 and 66 years, respectively). Overall, men with a first primary cancer were followed for a mean of 3.9 years (3 277 970 PYR), whereas men with breast cancer were followed for a mean of 5.6 years (10 033 PYR).

Among men with breast cancer, overall subsequent cancer risk was not increased (SIR = 0.99, 95% CI = 0.86 to 1.13) (Table 1). However, the risk of developing a contralateral second breast cancer was strongly elevated (SIR = 29.64, 95% CI = 15.48 to 52.41; AER = 12 per 10 000 PYR) (Table 1). All second breast cancers were histologically confirmed. Men with breast cancer also had an increased risk of skin melanoma (SIR = 2.41, 95% CI = 1.15 to 4.43) and a slightly decreased risk of lung cancer (SIR = 0.73, 95% CI = 0.49 to 1.06).

Men aged less than 50 years at the time of first breast cancer diagnosis had the highest relative risk of a contralateral second breast cancer (SIR = 110.29, 95% CI = 13.33 to 401.32) (Table 1). There were no major differences in the risk of second breast cancers associated with treatment modality received for the first breast cancer, with similar risks between men who received radiation (SIR = 37, 95% CI = 7.6 to 110) and those who did not (SIR = 28, 95% CI = 13 to 53). The 121 men who received both radiotherapy and chemotherapy had a statistically significantly elevated risk of second breast cancer (SIR = 212, 95% CI = 43 to 621); however, the SIR is based on only three case patients and has wide CIs. Laterality, time since first diagnosis, or calendar year period did not statistically significantly modify the risk of a second breast cancer.

The relative risk of second breast cancer was substantially higher among men (SIR = 29.6, 95% CI = 15 to 52) than among 263 370 women with first

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See "Notes" following "References."

Table 1. Observed and expected second cancers among 1788 men with a first primary breast cancer who were registered with SEER from 1973 through 1996*

Second primary site	Observed	Expected	SIR	95% CI†
Overall findings				
All malignancies‡	215	218.04	0.99	0.86 to 1.13
Buccal cavity	5	6.32	0.79	0.25 to 1.85
Digestive system	39	49.04	0.80	0.57 to 1.09
Stomach	6	6.05	0.99	0.36 to 2.16
Colon	18	21.40	0.84	0.50 to 1.33
Rectum	7	8.72	0.80	0.32 to 1.65
Liver, gallbladder, other biliary	5	3.30	1.51	0.49 to 3.54
Respiratory system	29	41.76	0.69	0.47 to 1.00
Lung, bronchus	28	38.11	0.73	0.49 to 1.06
Contralateral breast	12	0.40	29.64	15.48 to 52.41
Kidney, renal pelvis, ureter	4	5.30	0.76	0.20 to 1.93
Prostate	74	67.99	1.09	0.85 to 1.37
Bladder	20	15.30	1.31	0.80 to 2.02
Melanoma of the skin	10	4.15	2.41	1.15 to 4.43
Lymphoma	5	6.84	0.73	0.24 to 1.71
Risk of contralateral breast cancer by age and years since diagnosis				
Age at first primary diagnosis, y				
<50	2	0.02	110.29	13.33 to 461.32
50–59	3	0.06	47.50	9.70 to 139.16
60–69	4	0.13	29.75	8.04 to 76.43
≥70	3	0.19	15.87	3.23 to 46.39
Years since first primary diagnosis§				
<1	1	0.05	19.76	0.50 to 109.20
1–4	7	0.17	40.66	16.39 to 84.34
5–9	3	0.11	26.22	5.36 to 76.90
≥10	1	0.07	14.79	0.37 to 81.90

*Excluding the first 2 months after diagnosis of first primary cancer. SEER = Surveillance, Epidemiology, and End Results Program; SIR = standardized incidence ratio (observed/expected numbers of second cancers); CI = confidence interval.

†Exact two-sided 95% CI.

‡Excluding nonmelanoma skin cancer.

§Numbers of men with primary breast cancer at risk in each time interval and person-years at risk (PYR) in parentheses are as follows: <1 y, 1788 (1373 PYR); 1–4 y, 1546 (4548 PYR); 5–9 y, 808 (2731 PYR); ≥10 y, 333 (1381 PYR).

primary breast cancer (SIR = 1.8, 95% CI = 1.7 to 1.8; 9635 second cancers). However, the overall incidence (observed/PYR) of second breast cancer among women (58 per 10 000 PYR) far exceeded that among men (12 per 10 000 PYR). The risk of a contralateral second breast cancer was higher among women aged 50 years or younger at the time of diagnosis (SIR = 3.18, 95% CI = 3.06 to 3.30) than among older women (SIR = 1.51, 95% CI = 1.47 to 1.54).

Among men with a primary cancer other than breast cancer, there was no increased risk of subsequent breast cancer (SIR = 1.13, 95% CI = 0.95 to 1.33) (Table 2). In fact, for men with any specific primary cancer other than breast cancer, there was no increased risk of subsequent breast cancer (Table 2). Although not statistically significant, there was a twofold increased risk for subsequent breast cancer among men with melanoma (SIR = 2.00, 95% CI

= 0.86 to 3.94). Among 151 men who developed breast cancer as a second malignancy (after any first malignancy), two were diagnosed with a contralateral breast cancer, i.e., a third primary cancer, indicating an especially high risk

(SIR = 77.10, 95% CI = 9.23 to 277.84).

Our results indicate that men with breast cancer have a 30-fold increased risk of contralateral breast cancer, much greater than the two- to fourfold risk among women with breast cancer (10, 11). However, the absolute risk of contralateral breast cancer among men with breast cancer was much lower (0.1% per year) than among women (0.6% per year) (10,11). The risk of subsequent contralateral breast cancer was highest for men aged less than 50 years at the time of the first cancer diagnosis, which is consistent with studies of women with breast cancer (11–13).

Because information on family history or other risk factors is not available from the SEER database, we could not directly study etiology. However, our results, indicating an increased risk of contralateral breast cancer but not of other malignancies, suggest an influence of a factor or factors specific to breast cancer. Previous investigators have indicated that family history is one of the strongest risk factors for breast cancer among men and women (4–6,8,14). An increased risk of breast cancer in men has been demonstrated among families with a history of breast cancer in women, and the risk increases with the number of affected female relatives (5,6, 14). In addition, an increased risk of breast cancer among female offspring of men with breast cancer has been reported (15–17). These findings are consistent with the frequently detected germline BRCA2 mutations in men with breast cancer (18–20) or other constitutional factors (i.e., inherited or intrinsic features, such as a chromosomal anom-

Table 2. Observed and expected second breast cancers following selected first primary cancers among men who were registered with SEER from 1973 through 1996*

First primary site (No. of subjects/person-years)	Observed	Expected	SIR	95% CI†
All malignancies (848 863/3 277 970)‡	145	128.55	1.13	0.95 to 1.33
Buccal and pharynx (33 982/152 261)	7	5.13	1.37	0.55 to 2.81
Colon (70 478/316 041)	14	14.14	0.99	0.54 to 1.66
Rectum (37 394/167 846)	5	6.98	0.72	0.23 to 1.67
Bronchus and lung (139 903/218 079)	6	8.02	0.75	0.27 to 1.63
Prostate (226 465/1 020 936)	51	53.31	0.96	0.71 to 1.26
Bladder (57 523/321 884)	17	13.60	1.25	0.73 to 2.00
Kidney (18 886/81 389)	5	2.65	1.89	0.61 to 4.40
Melanoma of the skin (26 690/161 680)	8	4.00	2.00	0.86 to 3.94

*Excluding the first 2 months after diagnosis of first primary cancer. SEER = Surveillance, Epidemiology, and End Results Program; SIR = standardized incidence ratio (observed/expected numbers of second cancers); CI = confidence interval.

†Exact two-sided 95% CI.

‡Excluding nonmelanoma skin cancer.

ally or gene polymorphism) affecting androgen metabolism, such as Klinefelter's syndrome (8).

Our findings of the association between breast cancer and melanoma of the skin (seen in both directions) in men cannot be readily explained because the only recognized risk factors shared by these two cancers is high socioeconomic status (21,22). A similar relationship between breast cancer and melanoma of the skin has also been found in women (23–25). In men, no association was detected between breast cancer and prostate cancer, suggesting different etiologies for these two hormone-dependent cancers.

The strengths of our study include the relatively large number of cases, given the rarity of breast cancer in men, and that 97% of the subsequent cancers (including all 12 contralateral breast cancers) were histologically confirmed invasive cancers. Thus, it is unlikely that these cancers were misdiagnosed metastases. By contrast, the limitations of our registry-based analyses include imprecise data on treatments received, lack of information on potential confounding factors, and the potential for a detection bias in ascertainment of subsequent cancers. Moreover, because SEER patients who migrate outside SEER areas are not followed for subsequent cancer incidence, our findings are likely to be conservative.

In summary, our findings demonstrate that although the relative risk of contralateral breast cancer following breast cancer in men is substantial, especially among early onset cases, the AER is small. Indeed, less than 1% of the 1788 patients studied developed a contralateral breast cancer.

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NOTES

¹Editor's note: The Surveillance, Epidemiology, and End Results (SEER) Program is a set of geographically defined, population-based tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis. The SEER Program records all treatment given for the first course of therapy in broad categories, i.e., surgery, radiotherapy, chemotherapy, and hormonal therapy; therapy given subsequent to the first course is not recorded.

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